Phlegmasia Cerulea Dolens: *

A 10-Year Review

J. Manly Stallworth, M.D., Gilbert B. Bradham, M.D., Richard R. Kletke, M.D., Richard G. Price, Jr.,** M.D.

From the Department of Surgery, Medical College of South Carolina and Roper Hospital, Charleston, South Carolina

Phlegmasia cerulea dolens, although recognized 400 years ago,[15] continues to have a mortality rate of 25 per cent and an amputation incidence of 50 per cent.[45] The purpose of this study is to review 55 cases previously recorded in the literature between 1954 and 1964 and to report 14 additional cases. Each patient in this series was observed by at least one of the authors. Cases reported prior to 1954 have been reviewed by Moser.[45]

History

Following the first recognition of gangrene from venous thrombosis by Fabricius Hildanus in 1593,[15] it was nearly 300 years before Cruveilhier [9] described that this condition was produced only by extensive thrombosis of large and small veins. In 1859 and 1894 Heuter [28] and Gaillard [20] reported isolated cases. In 1924 Buerger [5] reiterated the massive venous occlusion theory and clarified the clinical picture. In 1937 Fontaine and deSouza-Pereira [18] showed that complete ligation of the venous circulation in the leg of the dog produced gangrene, as it was already known to do in the intestine. This phenomenon was reproduced unintentionally in man when the femoral vein was ligated and injected with a sclerosing agent [55] during a saphenous vein operation in 1949. Gregoire,[23] in 1938, described this condition as *phlegmasia cerulea dolens.*

In the early 1900's there were several case reports, some of which appeared to include arterial thrombosis in addition to venous occlusion. In 1939 DeBakey, Burch and Oschner [11] found that either chemical phlebitis or ligation of the iliofemoral vein produced severe arterial spasm which could be relieved by sympathectomy. They further demonstrated that similar arterial spasm was initiated when an exudate was produced by irritating chemicals injected adjacent to the veins. McMasters and Parsons [40] pointed out that in the absence of arterial pulsations the lymph flow was slow, while in the presence of pulsations the flow was rapid. Thus a generalized hypothesis implied a relationship of veins, arteries and lymph vessels in the extremity during an acute thrombotic process. It was shown that venous irritation by mechanical occlusion, inflammatory occlusion or perivenous inflammatory changes resulted not only in venostasis but also in severe arterial spasm which, in turn, could markedly impede the lymphatic return and cause fluid retention in the limbs of experimental animals.

Leriche,[34] however, thought that the edema was due to peripheral vasospasm and that sympathetic block relieved the edema. Laufman *et al.*,[33] utilizing the mi-

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** Present address: Beaufort, South Carolina.

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croscopic observation technics of Kniseley,[31, 32] studied the intravascular cellular flow following experimental vascular occlusion in the mesenteric vessels and demonstrated that there was moderate dilation of tributary veins and marked spasm (up to ⅛ original caliber) of associated arteries. The capillaries, while usually markedly dilated, were occasionally narrowed as if they were in spasm. After venous occlusion was released the arteries remained in spasm. During prolonged venous occlusion there were increased aggregates of red blood cells, followed by clumping and intravascular thrombosis of both arteries and veins.

In 1951 Veal and associates [56] restudied the effects of major vein occlusion in the mesentery of dogs and observed that after one hour of venous occlusion, venous pressure reached 865 mm. water and the bowel became "deep purple, edematous and petechial. Hemorrhages were present throughout the mesentery." Arterial pressure was maintained but pulsations were "hardly demonstrable . . . the arterial system remained open and spasm did not develop. The blood flow came to a standstill when the venous pressure reached its peak."

Methods and Materials

Clinical Picture

The classical picture of phlegmasia cerulea dolens as demonstrated in the 69 patients reported is sudden pain (75%) in the involved extremity followed by swelling and a blue-violet color in the skin (Fig. 1). In one fourth of the cases, the onset of the triad of symptoms was gradual (Table 1).

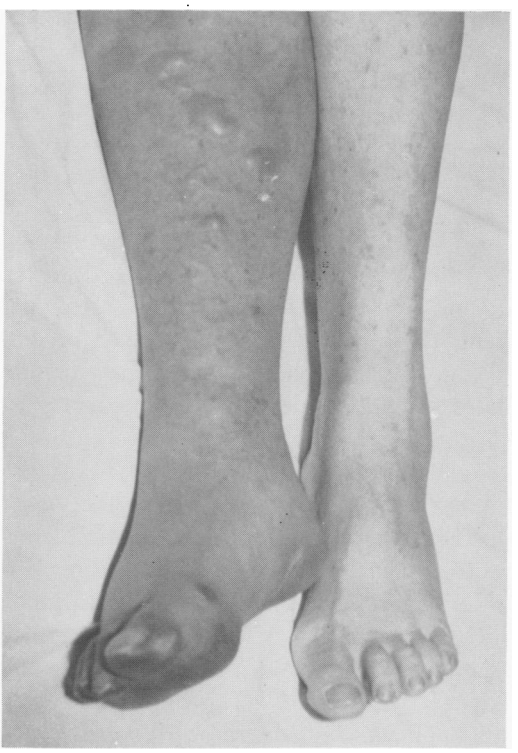

FIG. 1. F. M., 57-year-old woman with early phlegmasia cerulea dolens, showing violet discoloration swelling, early bullae formation and impending gangrene of the toes.

The disease occurs most frequently between the ages of 40 to 49, (Fig. 2) and is equally prevalent among men and women. There were no Negro patients among the 69 cases with phlegmasia cerulea dolens.

More than 91% of patients (Table 2) described some form of thrombophlebitis, disease or operation immediately preceding the onset of acute symptoms. About one fourth gave a history of chronic thrombophlebitis while another one fourth described acute phlegmasia alba dolens as

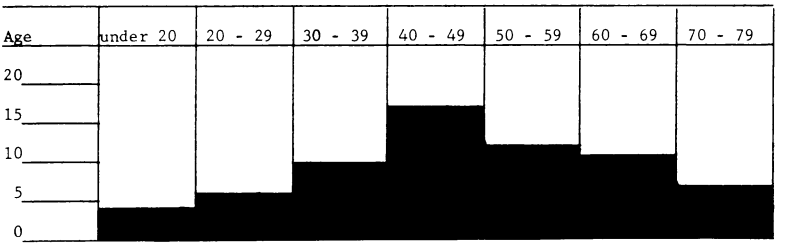

FIG. 2. Incidence according to age and sex. There were 34 males and 34 females (sex not mentioned in one report).

TABLE 1. *Occurrence of Symptoms: Pain, Edema and Cyanosis*

Occurrence	Prev. Cases	Pres. Series	Total	Av. %
Gradual onset	12	5	17	24.7
Sudden onset	43	9	52	75.3

the forerunner of phlegmasia cerulea dolens. In approximately 50% of the patients there was a history of cancer, ulcerative colitis, pneumonia, heart failure, diabetes or tuberculosis as antecedent diseases. A history of recent operations was present in 20% of the patients. (Many patients describe carcinoma and operation or phlebitis and operation as concomitant disorders.) No history of any preceding disorder was reported by 8.7% of the patients.

On examination, the extremity is blue, edematous and painful in practically all (over 95%) patients (Table 3). Some show signs of varying degrees of shock since enormous quantities of fluid may be trapped in the involved part. Often the massive edema prevents adequate detection of distal pulses which may account, in part, for the absence of pulsations in about 52% of patients. On the other hand, these pulse findings may be a distinguishing feature of the disease. About 88% of the patients are described as having coolness of the involved extremity.

As the process continues, bullae may develop and para-esthesias or motor paralysis may ensue (Fig. 3A). Renal damage or failure may follow rapidly as the anoxic process extends. If death does not prevail, gangrene (Fig. 3B) of varying degree develops in about 31.9% of patients (Table 4), resulting in major amputation (Fig. 3C). Of the entire group, 29% show evidence of pulmonary emboli, but only 7.2% died as a result of the emboli. Approximately 46.8% of the survivors develop the typical post-phlebitic syndrome (Table 4). Included in this group are those who had non-fatal pulmonary emboli or tissue loss or both.

At any stage the acute process may subside spontaneously or be aborted by supportive measures. Death occurred in 31.9% of the patients (Table 5); the major single cause was advanced cancer (36.3%), yet this severe type of phlebitis and its complications accounted for 49.9% of the deaths.

Treatment

The management of patients with phlegmasia cerulea dolens has been rather loosely categorized, and combinations of methods have made accurate appraisal of treatment impossible. However the impressions have been summarized in Tables 6 and 7.

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TABLE 2. *Antecedent Conditions*

Conditions	Prev. Cases	Pres. Series	Total	Av. %
Chronic phlebitis	17	3	20	28.9
Acute phlebitis	12	4	16	23.2
Disease*	29	6	35	50.7
Operation	13	1	14	20.3
(Total)				(91.3)
None	2	4	6	8.7

* Cancer, ulcerative colitis, pneumonia, heart failure, diabetes or tuberculosis.

TABLE 3. *Physical Findings*

Findings	Prev. Cases	Pres. Series	Total	Av. %
Blue discoloration	55	14	69	100
Edema	53	14	67	97.1
Pain	53	13	66	95.6
Pulses present	23	11	34	49.3
Pulses absent	32	3	35	51.7
Decreased skin temp.	47	14	61	88.4

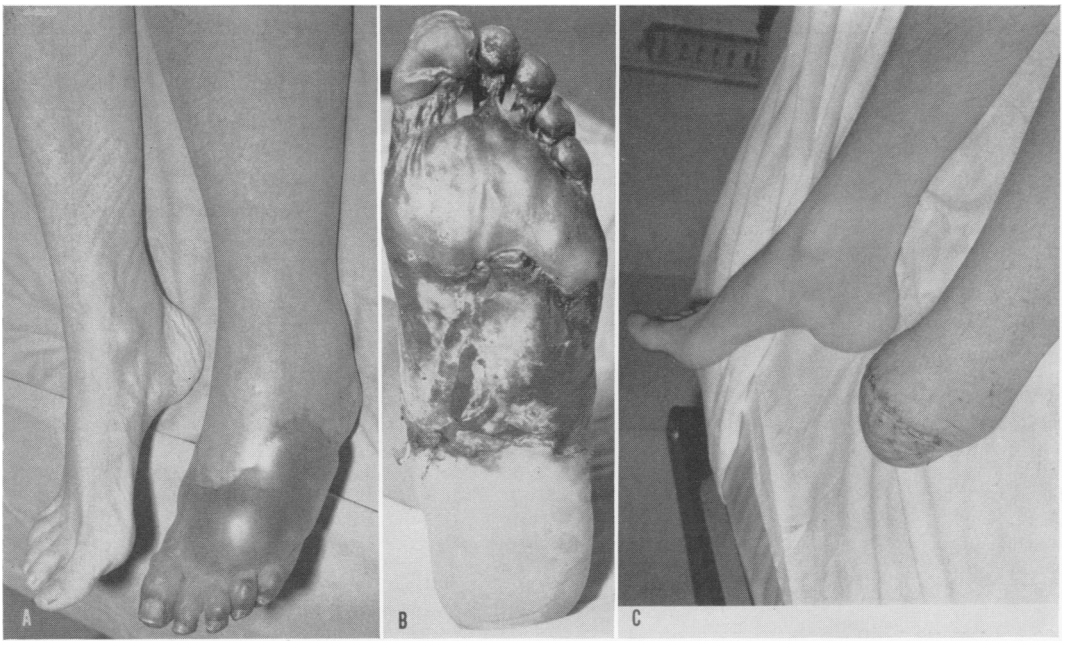

FIG. 3. A. A. C., 39-year-old woman. Advancing stage of phlegmasia cerulea dolens, showing early gangrene of toes and advanced bullae formation. B. Progression of disease showing frank gangrene of toes and forefoot C. Symes amputation. End result of disease process seen in A and B.

structed venous flow was generally practiced (73.9%).

Heparin was used in 81.3% of the cases studied. Ordinarily its use was avoided when bleeding from a concomitant disease, such as ulcerative colitis, existed. It was used in nonoperative treatment to prevent propagation of the clot and in postoperative management to prevent reformation of clot.

Exercise, both active and passive, was advocated by Veal [56] in 1957. In the present study seven patients were treated in this manner, three of whom sustained fatal pulmonary emboli. Of the survivors two had post-phlebitic symptoms.

Sympathetic blockade—as first recommended by Leriche [35] and later by De-

TABLE 4. *Results*

Results	Prev. Cases	Pres. Series	Total	Av. %
No residual	15	2	17	36.2**
Post-phlebitic syndrome†	18	4	22	46.8**
Loss of tissue*	11	4	15	31.9**
Pulmonary emboli	13	7	20	29.0***
Death	16	6	22	31.9

* Gangrene in varying degree.
** % of those living.
*** % of total; 7.2% died.
† Including those with loss of tissue and nonfatal pulmonary emboli.

TABLE 5. *Associated Diseases as Cause of Death*

Causes	Prev. Cases	Pres. Series	Total	Av. %
Pulmonary emboli	4	1	5	22.7
Metastatic disease	7	1	8	36.3
Phlegmasia cerulea dolens	4	2	6	27.2
Myocardial infarction		1	1	4.5
Bleeding diathesis		1	1	4.5
None given	1		1	4.5
Total	16	6	22	31.9

TABLE 6. *Types of Treatment in Total Series of Patients*

Treatment	No Residual	Post Phlebitis	Tissue Loss	Death	Emboli	Total	Av. %
Heparin, elevation	3	2	3	7	3	14	20.2
Heparin, elevation, exercise	2	2	0	3	3	7	10.1
Heparin, elevation, block	4	5	3	2	2	13	18.8
Heparin, elevation, block, vasodilator	3	1	4	2	2	9	13.0
Heparin, block, thrombectomy	1	2	1	0	1	3	4.3
Heparin, thrombectomy, ligation	2	1	0	0	1	3	4.3
Heparin, thrombectomy, ligation, block	0	1	0	0	0	1	1.4
Heparin, block, fasciotomy, vasodilator	0	0	0	1	1	1	1.4
Heparin, thrombectomy	0	0	2	3	2	4	5.7
Heparin, fasciotomy	0	1	0	0	0	1	1.4
Elevation, ligation	0	1	0	0	1	1	1.4
Elevation, ligation, block	0	1	0	0	0	1	1.4
Elevation, thrombectomy, ligation, block	1	0	0	0	0	1	1.4
Elevation, thrombectomy, ligation, and vasodilators	1	2	1	1	2	5	7.2
Thrombectomy	0	0	0	1	1	1	1.4
Block, ice pack	0	0	0	1	1	1	1.4
Vasodilators	0	2	0	1	0	2	2.8
Not specified	0	1	1	0	0	1	1.4
Total	17	22	15	22	20	69	100.0

Bakey,[12] Edwards [14] and others—was effected as a lumbar sympathetic block, spinal anesthesia or caudal anesthesia. Those patients treated by nerve block within 6 hours of onset showed very good results, not only temporarily but, at times, permanently when the process was rather dramatically reverted from phlegmasia cerulea dolens to phlegmasia alba dolens. Even in the later stages, after demarkation of gangrenous parts was partially delineated, sympathetic interruption often relieved pain and produced clinical evidence of increased blood flow to the level of tissue loss. Where the process had extended farther, nerve block was useless. In 30 patients who received sympathetic block, either alone or in combination with other measures, the mortality was 20%. In 33% of cases there resulted a postphlebitic syndrome and in 30% there was no residue.

TABLE 7. *Summary of Types of Treatment*

Treatment (alone or with other methods)	No. Patients	%
Elevation	51	73.9
Heparin	56	81.3
Exercise	7	10.1
Sympathectic block	30	43.5
Vasodilators	17	24.6
Thrombectomy & ligation	27	39.1
Thrombectomy	8	11.6
Fasciotomy	2	2.9

Vasodilation as a form of treatment has varied from reflex heating methods to chemicals such as alcohol, Priscoline®, Ilidar®, nicotinic acid, papaverine, etc. In several instances, Priscoline® given intra-arterially and Ilidar® given intravenously seemingly improved the color and temperature of the extremity. Otherwise the results appeared equivocal.

Thrombectomy with central ligation of drainage veins, as advocated by DeBakey [12] in 1949, has in the past 10 years been used along with various other nonoperative methods of treatment in 27 instances. There were three deaths (11%). Four patients (15%) survived without residual disease. In these 27 patients the surgical measures included ligation of the vein, not only adjacent to the clot but also at higher levels,

such as vena cava ligation followed by common femoral thrombectomy.

In addition to this group, there were two patients who had venous ligation without thrombectomy. Both survived but had the typical postphlebitic syndrome.

Thrombectomy—as recommended previously by Mahorner,[36] Haller,[25] Fogerty[16] and others—without venous ligation, but in combination with various other methods of treatment, was used in eight instances. There were four deaths and only one patient lived without residual damage.

Fasciotomy as a means of relieving tissue tension was tried several times along with many other forms of treatment. Results are difficult to evaluate, but each author believed that the diminished tissue tension afforded evidence of improvement, although sometimes only temporary.

Medicinal therapy such as cortisone, fibrinolysin, Butazolidin®, antibiotics, etc.,

TABLE 8. *Summary of Patients on Present Series*

Name	Age Sex	Symptoms	Past History	Examination	Treatment	Result (cause of death)
E. A.	76 F	Gradual pain, edema, blue, cold, (3 extremities)	Chronic phlebitis, Ca gall bladder (found at autopsy)	Pain, edema, blue, cold, pulses +	Block, heparin, fibrinolysin, cortisone	Tissue loss, B-K amp. (bilat.)
S. C.	45 M	Sudden pain, edema, blue, cool	Operation	Pain, edema, blue, cool, pulses +	Thrombectomy attempted, pulm. emboli in OR	Death (bleeding diathesis following pulm. embolectomy, pulm. emboli)
A. C.	39 F	Gradual pain, edema, blue, cool	Acute phlebitis, broken ankle	Pain, edema, blue, cool, pulses +	Block, heparin, elevation, vasodil.	Tissue loss, Symes amp.
J. E.	56 M	Sudden pain, blue, edema, numbness	None related	Pain, edema, blue, cold, pulses +	Block, heparin, elevation	Post-phlebitic syndrome (mild)
F. F.	57 F	Sudden edema, blue, cool	Diabetes, lupus erythematosis	Edema, blue, cool, pulses +, no pain	Thrombectomy, heparin, cortisone	Death (myocard. infarct) pulm. emboli (incidental)
A. G.	59 M	Sudden pain, edema, blue, cool	None related	Pain, edema, blue, cool, pulses +	Block, heparin, vasodilators	Death (phlebitis and pulm. emboli)
L. H.	20 F	Gradual pain, edema, blue, cool	Acute phlebitis	Pain, edema, blue, cool, pulses −	Block, heparin, elev., vasodil., fasciotomy	Death (renal fail.-tissue necrosis, limb)
F. M.	57 F	Sudden pain, edema, blue, cold	Acute phlebitis, diabetes (cont'd)	Pain, edema, blue, cold, pulses −	Block	Death (metastatic Ca) pulm. emboli (incidental)
T. McA.	55 M	Sudden pain, edema, blue, cold	Chronic phlebitis, operation	Pain, edema, blue, cool, pulses +	Block, heparin, thrombectomy	Post-phlebitic syndrome (moderate)
W. R.	19 M	Sudden pain, edema, blue, cool	Chronic phlebitis, old pulm. emboli	Pain, edema, blue, cool, pulses +	Block, heparin, vasodil., thrombect, elevation	Post-phlebitic syndrome, tissue loss, skin graft, pulm. emboli
W. S.	19 M	Gradual pain, edema, blue, cool	None related	Pain, edema, blue-red, cool, pulses +	Block, heparin, cortisone, vasodil.	Complete recovery
K. V.	49 M	Sudden pain, edema, blue, cool	None related	Pain, edema, blue, cool, pulses −	Treated elsewhere	Tissue loss, toe amp.
P. W.	76 F	Gradual pain, edema, blue, cool	Congestive heart failure	Pain, edema, blue, cool, pulses +	Block, heparin, elevation	Death (pulm. emboli)
J. W.	29 F	Sudden pain, edema, blue, numb	Acute phlebitis after pneumonia	Pain, edema, blue, cool, pulses −	Block, heparin, elevation, vasodilators	Complete recovery

could not be appraised accurately. In individual instances cortisone or antibiotics were used to treat associated diseases.

Transfusion and other forms of supportive treatment were often used, especially when there was acute loss of fluid in the edematous limb.

Discussion

The cause of phlegmasia cerulea dolens is unknown, but accumulated data afford certain theoretical impressions. Massive venous occlusion, no matter what the etiology, produces marked venous pressure elevation locally,[14, 56] concomitant venous dilatation,[33] sludge formation and minute propagating thrombi.[33] There is arterial spasm[12, 33] without changes in arterial blood pressure,[56] but with marked diminution of arterial flow * resulting in ischemia of the capillary system and producing an abnormal escape of fluid and red blood cells. With diminished blood flow there is slowed lymphatic return,[40] thus aiding in the retention of fluid. If tissue tension from swelling exceeds arterial pressure, additional ischemia results.

When the major venous occlusion is released experimentally, associated venous pressure returns to normal, but diminished arterial flow tends to remain lowered. Since inflow arterial blood pressure remains unchanged and outflow venous pressure reflects only mechanical obstruction, there appears to be some partial obstructive force in smaller vessels. Whether this is arterial or venous in origin is conjectural. There is obvious venostasis in capillaries and venules as shown by blue skin or bowel. The entire process can be established in a shorter time than is needed for normal *in vivo* clotting. Impedence to blood flow could be due to sludging and ultimate clotting of red blood cells in smaller vessels or to small vessel spasm or both. If the latter prevails, the theory of sympathetic block is supported from a physiologic aspect. In addition, the recent operative approach—removal of the major thrombus—actually reverses the process originally instigating the massive venous occlusion. Obviously, if progressive venous occlusion and vasospasm are not relieved before tissue necrosis occurs, neither thrombectomy, sympathetic block nor any other method of treatment will help.

In some instances of massive carcinomatosis, no combination of methods of treatment was affective; however, in uncomplicated cases, evacuation of the forward clot and release of vasospasm appeared paramount in preventing harmful sequelae.

The importance of heparin and, to a lesser degree, vasodilators, is well established. Elevation of the diseased parts to promote gravity drainage is sound.

Exercise in the presence of unfixed blood clot has resulted in a high rate of pulmonary embolus and death. In the case of operative thrombectomy, this embolic phenomenon is apparent when passive motion is used to effectively expel distal clot. The physical action of muscle tension propels centrally, not only blood but also any floating object in it.

There had been some underlying disease process or recent operation in 91.3% of all patients. Strict precautionary measures designed to prevent venostasis and to promote venous return to the heart are indicated. This is especially true in postoperative patients and in those with either acute thrombophlebitis or sequelae of chronic phlebitis. In two patients the application of heat to the early acute phlebitic limb was believed to have increased swelling and probably aided in conversion from phlegmasia alba dolens to phlegmasia cerulea dolens. Severe pain accompanying the usual phlebitis may be the first sign of impending massive thrombosis. Early decision regarding anticoagulants, sympahtetic block, thrombectomy, etc. is strongly indicated if the thrombotic process is to be relieved before tissue necrosis occurs.

* This experimental work to be published later.

The possibility of venous and arterial spasm in addition to the obvious venous thrombosis has been debated for centuries. In the present review many dramatic conversions from the *blue* phlebitis to ordinary *white* phlebitis have been noted to follow sympathetic interruption. Pain, in almost all instances, was relieved or improved whether or not tissue necrosis was present. Return of warmth to the skin was sometimes only transient. Best results from sympathetic block were derived during the first 6 hours after onset of the acute phase.

Thrombectomy, as recommended by many authors,[12, 14, 16, 36] has also yielded many excellent results. Failures, which occurred about as often as successes, appear to have been due to reformation of clot, pulmonary emboli and inability to remove clots from tributary veins. Thrombectomy after venous ligation, while popular as a form of treatment in the early part of the past decade, has recently been replaced almost entirely by thrombectomy alone. There was no reported instance where partial occlusion of the vena cava was practiced in this series of patients, although total occlusion was performed several times with satisfactory results.

The principles of treatment appear to be as follows:

1. Recognize the disorder which precedes the phlebitis and meticulously prevent venostasis.
2. Relieve venous and arterial spasm by some form of sympathetic blockade.
3. Promote venous return by elevation of the involved parts in relationship to the level of the heart.
4. Remove major offending thrombus when possible.
5. Be prepared to partially or completely occlude the vena cava when there is evidence of pulmonary emboli.
6. Prevent additional thrombosis by maintaining adequate heparin levels.
7. Amputate gangrenous tissue early using refrigeration anesthesia and tourniquet when indicated in preparation for amputation.[30]

Summary

During the past 10 years, 55 patients with phlegmasia cerulea dolens have been reported. In the same interval 14 additional patients were observed by the authors. These 69 patients comprise the basis for the present study.

Despite the recent advances in treatment of vascular diseases, the basic physiopathologic differences between phlegmasia alba dolens and phlegmasia cerulea dolens are not entirely understood. There is, unequivocally, massive venous occlusion, but there must be other factors, since at times spontaneous recovery and dramatic improvement follow thrombectomy, simple ligation of the vena cava or sympathetic blockade. The exact causes of ischemia and gangrene are conjectural, but obstruction to blood flow at the arteriole-capillary-venule level is probably a factor. This obstruction may be due to spasm of the vessels or stasis thrombosis or both.

Since the occlusive process may involve more than one venous system in distant parts of the body and is often associated with malignant disease there may be an associated but unrecognized chemical reaction.

Regardless of the type of treatment, the overall mortality is 31.9%. Of surviving patients, 31.9% lose tissue and 46.8% have post-phlebitic syndrome. Once the disorder is recognized, the described principles of management should be observed.

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Discussion

Dr. Mark M. Ravitch (Baltimore): This is an extraordinary clinical phenomenon which Dr. Stallworth has described so elegantly. I would like to report on a recent experience of Dr. Richard W. Steenburg with a patient at the Baltimore City Hospital, a young woman who had severe and extensive burns, who developed a perfectly classical picture of sudden pain with a great blue-violet swollen leg. A thrombectomy was done immediately, but the observation was made that the femoral artery appeared not to be pulsating. It was incised and a well-organized thrombus was removed from it.

She did well, and we have been wondering ever since, if this is an isolated observation or if—for instance in a series like Dr. Stallworth's—there is evidence (arteriographic or postmortem dissection evidence) to show that this occurs occasionally, never or often.

Dr. Robert P. McBurney (Memphis): I would like to ask Dr. Stallworth a question. He had eight cases in which he used the thrombectomy technic described by Mahorner, Heller and others, with four deaths, and I wondered if he would give us some more details on those deaths. I believe that this is the preferred treatment of this condition, having used it in three cases. All of my three cases have been early cases, to be sure, but each has been a gratifying success.

If he creates the impression that there is a 50% mortality with this treatment, I think it might discredit what I think probably is the best treatment.

Dr. J. Manly Stallworth (closing): I think perhaps this slide will answer Dr. Ravitch's question, at least in the experimental lab. This experiment has been used for a number of years, beginning in the 1800's, repeated again in 1951 by Dr. Veal and here we have added nothing more to it than the flow meter. The pressure transducer is attached to the proximal artery going into an isolated segment of the bowel, a venous catheter is inserted for pressure, and a flow meter probe is placed on an artery in the isolated mesentery. The vein is intermittently occluded and a rather amazing series of events takes place. The bowel becomes violently blue within a few minutes, the veins become quite dilated, the capillaries are markedly distended, whereas the arterioles become somewhat more narrowed as though in spasm. The flow virtually stops as time goes on.

The next slide shows the tracing from a dog experiment in which in the upper level, one sees the measured mesentery artery flow, in the second line the mesentery artery pressure, and in the third line the mesentery venous pressure. As the vein is occluded, one can see that the mesenteric artery flow is markedly diminished and goes almost to the zero point where it is maintained until the vein is released; then it becomes elevated but not quite to the point of flow that was existent before.

If this period of occlusion is allowed to remain for half an hour, the return of arterial flow is quite slow. If the clamp stays on longer, this flow is zero, even though the mesentery artery pressure at this time remains constant. The artery pulse seems to be normal, but there is no forward flow of blood. At the same time the venous pressure, interestingly enough, within 2 minutes will approach that of the mean artery pressure, and is maintained until the vein is released.

If this clamp remains on the mesenteric veins for a sufficient length of time, all vessels are occluded by thrombus, and I imagine this is what happened in Dr. Ravitch's patient.

As to Dr. McBurney's comment, it was not my intent to condemn any procedure. I am simply reporting what has been described in the literature up to the present time. There were four deaths among those 8 patients who had thrombectomies, and who did not have an associated venous ligation. Three of these deaths were due to emboli, and the fourth was one of our own group of patients who developed pulmonary embolus, while his leg was being prepared in the operating room for thrombectomy. His chest was opened, he was connected to a hear-lung pump, the clot was removed, but the patient, unfortunately, had some type of bleeding diathesis, and continued to hemorrhage from all sources over the next 3 or 4 hours. He subsequently died. His death was due to some type of clotting phenomenon, which was not controllable.